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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,797	05/16/2001	James L. Hartley	0942.285000G	2106

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

TH

Office Action Summary	Application No.	Applicant(s)	
	09/855,797	HARTLEY ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	wsf

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-59,61-68 and 71-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-59, 61-68 and 71-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 9/28/2006. Claims 52-59, 61-68 and 71-78 are pending and under examination in the instant Office action.

Any rejection made in the previous Office action not set forth herein is hereby withdrawn.

Claim Objections

Claims 72-74 and 76-78 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 72 recites "[t]he method of claim 71, wherein said two or more site-specific recombination sites are selected from the group consisting of *lox* sites, lambdoid *att* sites and mutants and variants thereof" in lines 1-3 (emphasis added). Claim 72 is objected to because mutants and variants of *lox* sites/lamboid *att* sites are not defined and can thus encompass any recombination site with any number of insertions, deletions or substitutions, i.e. ANY recombination site. As such, claim 72 as well as claims 73-74 & 76-78, which

also recite "mutants and variants" of several recombination sites, fail to further limit the claim(s) from which they are dependent.

Claim 73 is also objected to because of the following informalities: claim 73 does not end in a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52-59, 61, 71 & 75, and therefore dependent claims 62-68, 72-74 & 76-78, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. **This is a new rejection not necessitated by Applicant's amendment.**

Claim 52 recites "[a]n *in vitro* method for synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites" in lines 1-2 (emphasis added). Claim 52 is vague and indefinite in that the metes and bounds of a "site-specific recombination site" are unclear. Does

Applicant intend nucleic acids which comprise any site which can be used for recombination at that site such as restriction sites, endo- and exonuclease sites as well as lox sites; or does Applicant intend sites which are limited to recombination mediated by site-specific recombination proteins such Cre, Int, IHF, Xis and Fis as listed in claim 64?

Similarly, claims 59, 61, 71 and 75 are vague and indefinite because they recite "site-specific recombination sites" and the metes and bounds of a "site-specific recombination sites" are unclear as explained above.

Claim 52 recites the limitation "said linear nucleic acid molecule" in line 9. There is insufficient antecedent basis for this limitation in the claim. Does Applicant intend said at least one isolated linear nucleic acid molecule as recited in step "a" of the claim, or does Applicant intend "said linear nucleic acid molecule as generated in and recited in step "b" of the claim?

Similarly, claims 53-58 recite "said linear nucleic acid molecule." Does Applicant intend said at least one isolated linear nucleic acid molecule as recited in step "a" of the claim, or does Applicant intend "said linear nucleic acid molecule" as generated in and recited in step "b" of the claim?

Claims 52-59, 61-68 and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection. This is a new rejection not necessitated by Applicant's amendment.**

The specification as originally filed does not provide support for the invention as now claimed: "[a]n *in vitro* method for synthesizing one or more nucleic acid molecules comprising one or more site-specific recombination sites" (claims 52-59, 61-68 and 71-78; emphasis added). The specification does not provide sufficient blazemarks nor direction for the instant nucleic acid sequences encompassed by the above-mentioned limitation, as currently recited. The instant claims now recite a limitation, which was not clearly disclosed in the specification as filed, and now changes the scope of the instant disclosure as filed. Such a limitation recited in the present claims, which did not appear in the specification as filed, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 71 and 75 are rejected under 35 U.S.C. 102(a and e) as being anticipated by Auerbach (US Patent 5,614,389; IDS Ref. AJ1). **This is a new rejection not necessitated by Applicant's amendment.**

Note: For purposes of this rejection only, Examiner has interpreted "site-specification recombination site" to include any nucleic acid sequence purposely engineered such that recombination may occur at that site, including through the use of restriction enzymes sites, sites of DNA repair proteins and or sites of DNA homologous recombination.

Auerbach teaches methods for amplifying a nucleic acid molecule which employs a single primer and in which the

amplification is performed under isothermal conditions. The single primer is preferably employed in concert with a target polynucleotide which has been adapted to be part of a circular double-stranded DNA molecule that comprises: (a) a lox site; (b) the target polynucleotide region; and (c) a hemi-modified restriction site located between the target polynucleotide region and the lox site (see column 17, lines 44-57). In one embodiment, the double-stranded circular molecule is obtained via Cre-mediated recombination of a linear double-stranded DNA molecule that comprises: (a) a first lox site located at a first end of the linear molecule; (b) a second lox site located at a second end of the linear molecule, wherein the first and the second lox sites are directly oriented with respect to one another so as to permit Cre to mediate the circularization of the linear double-stranded molecules; (c) the target polynucleotide region located internal to the first and second lox sites; and (d) a hemi-modified restriction site located between the target polynucleotide region and one of the lox sites (column 18, lines 11-29). To obtain such linear molecules, Auerbach teaches that a starting linear double-stranded nucleic acid molecule may be incubated in the presence of ligase (i.e. *in vitro*) and double-stranded "adaptor molecules" containing the desired sequence(s): lox sites and

hemi-modified restriction sites. Although Auerbach teaches that the *lox* sites recombine to form a circular molecule, the lox sites do not recombine with the hemi-modified restriction sites; thus Auerbach teaches all the claim limitations of claims 71 and 75.

Claims 52, 56, 61-66 are rejected under 35 U.S.C. 102(e) as being anticipated by Elledge et al (US Patent 5,851,808; IDS Ref AD3). **This is a new rejection not necessitated by Applicant's amendment.**

Elledge et al teach methods for the rapid subcloning of nucleic acid sequences both *in vivo* and *in vitro* without the need to use restriction enzymes (see entire document, especially column 1, lines 55-67). Elledge et al teach the *in vitro* recombination of two nucleic acid constructs, each comprising a site-specific recombination site. The site-specific recombination sites do not need to be the same as long as the sequences can recombine with one another (see, e.g. column 4, lines 9-14 and 28-41). In a preferred embodiment, Elledge et al teach that a gene of interest from a cDNA library can be cloned into a pUNI vector comprising, e.g., a loxP site. Then the pUNI vector can be recombined with a pHOST vector comprising a second loxP site such that the expression of the gene of interest is

placed under the control of the promoter contained within the pHOST expression vector (see column 12, lines 52-67 and column 13, lines 1-19). At column 17, lines 45-47, Ellegde et al teach that the fusion of a pUNI vector and a pHOST vector may be accomplished *in vitro* using a purified preparation of a site-specific recombination protein such as Cre. In a particular subembodiment, Elledge et al teach that a linker containing a loxP site can be ligated to the ends of a linearized pHOST vector utilizing compatible sticky ends designed into the adapter (see column 21, lines 21-52). Thus Elledge et al teach the claims limitations of claim 52: obtaining at least one isolated linear nucleic acid molecule (the linearized pHOST vector which requires modification); contacting said molecule *in vitro* with one or more adapters comprising at least a first site-specific recombination site under conditions sufficient to add one or more of said adapters to one or more termini of said linear nucleic acid molecule (addition of the linker to the linearized pHOST vector); and mixing of the modified vector with at least one (other) vector comprising a second site-specific recombination site in the presence of a site-specific recombination protein under conditions sufficient to cause recombination between said first and second site-specific recombination sites and wherein the site-specific recombination

protein mediates said recombination. Regarding claim 61, Elledge et al teach such a method wherein said first and/or second site-specific recombination sites or portions thereof are engineered site-specific recombination sites. Regarding claims 62-66, Elledge et al teach such methods comprising the use of lox and lambdoid att sites and the use of recombination proteins including Cre and integrases (see, e.g., column 2, lines 36-42; column 15, lines 36-46; and column 16, lines 6-26).

Response to Arguments

Any response to Applicant's arguments has been rendered moot in light of the withdrawal of the previous rejections and the new grounds of rejection recited herein.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy

should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

December 4, 2006

NANCY VOGEL
PRIMARY EXAMINER